UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/526,730	09/16/2005	Evert Johannes Bunschoten	0470-050738	1144

7590 09/17/2007

William H Logsdon
Webb Ziesenheim Logsdon Orkin & Hanson
700 Koppers Building
436 Seventh Avenue
Pittsburgh, PA 15219-1818

EXAMINER	
JAVANMARD, SAHAR	
ART UNIT	**PAPER NUMBER**
1609	

MAIL DATE	DELIVERY MODE
09/17/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/526,730	BUNSCHOTEN ET AL.	
	Examiner	Art Unit	
	SAHAR JAVANMARD	1609	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 March 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *14 October 2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The Office Action is in response to the 371 of PCT/NL03/00621 filed September 5, 2003 Claims 1-16 have been cancelled, and claims 17-31 have been entered by preliminary amendment filed March 4, 2005. Claims 17-31 are pending. Amended claims 17-31 are being examined on the merits herein.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

For the sake of compact prosecution, the Examiner is assuming the diseases cited in claim 31, are the same diseases intended to be treated in claim 28.

Claims 1-28 rejected under 35 U.S.C. 112, first paragraph, for scope of enablement because the specification, while being enabling for the treatment of androgen deficiency, does not reasonably provide enablement for treating all of the following diseases: hormonal contraception, wasting syndrome, anti-retroviral drug induced lipodystrophia, lack of well-being or fatigue in HIV infected individuals, reversing catabolic state caused by a chronic illness, surgical intervention, oncological condition, trauma and/or malnutrition; a leydig cell dysfunction and germinal epithelial damage following cytotoxic chemotherapy, fatigue or maintaining weight, hemoglobin or

neutrophil count during or subsequent to cytotoxic chemotherapy or radiotherapy benign gynecological disorders; improving libido; delayed puberty; or supporting female-to-male conversion as recited in these claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. The specification does not provide sufficient information that all of the diseases set forth in claim 31 are treatable by the administration of an androgenic steroid selected from the group consisting of 15-hydroxytestosterones, 16-hydroxytestosterones and precursors thereof, as described in the methods claimed.

The instant specification fails to provide information that would allow the skilled artisan to fully practice the instant invention without undue experimentation. Attention is directed to *In re Wands*, 8USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547, the court recited eight factors:

(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

The Nature of the Invention:

All of the rejected claims are drawn to an invention that pertains to a method of

treatment with an androgenic steroid selected from the group consisting of 15-hydroxytestosterones, 16-hydroxytestosterones and precursors thereof for the treatment of a wide array of diseases set forth in claim 31. The nature of the invention is complex in that it encompasses the treatment of a multitude of diseases.

Breadth of the Claims:

The complex nature of the subject matter of this invention is greatly exacerbated by the breadth of the claims. The claims encompass treatment of a multitude of diseases with the administration of an androgenic steroid selected from the group consisting of 15-hydroxytestosterones, 16-hydroxytestosterones and precursors thereof.

Guidance of the Specification:

The guidance given by the specification as to how one would administer the claimed compounds to a subject in order to inhibit any of these diseases is limited. All of the guidance provided by the specification is directed toward determining androgen potency, including a competitive steroid binding assay was used to determine the relative binding affinity of 15α-hydroxytestosterone, 15β- hydroxytestosterone, and 16β-hydroxytestosterone to the androgen receptor (AR); an assay to determine *in vivo* androgenic potency; and a competitive steroid-binding assay.

Working Examples:

Applicant provides an *in vitro* steroid binding assay used to determine the relative

binding affinity of 15α-hydroxytestosterone, 15β- hydroxytestosterone, and 16β-hydroxytestosterone to the androgen receptor (AR); an assay to determine *in vivo* androgenic potency; and an *in vitro* competitive steroid-binding assay

State of the Art.

While the state of the art is relatively high with regard to treating androgen deficiency,

the state of the art with regard to treating the multitude of diseases set forth in claim 31 with the administration of an androgenic steroid selected from the group consisting of 15-hydroxytestosterones, 16-hydroxytestosterones and precursors thereof is underdeveloped. There is no such thing as a treatment of these generally because of their diversity. Thus, it is beyond the skill of one skilled in the art today to get an agent to be effective in treating hormonal contraception, wasting syndrome, anti-retroviral drug induced lipodystrophia, lack of well-being or fatigue in HIV infected individuals, reversing catabolic state caused by a chronic illness, surgical intervention, oncological condition, trauma and/or malnutrition; a leydig cell dysfunction and germinal epithelial damage following cytotoxic chemotherapy, fatigue or maintaining weight, hemoglobin or neutrophil count during or subsequent to cytotoxic chemotherapy or radiotherapy benign gynecological disorders; improving libido; delayed puberty; or supporting female-to-male conversion, evidence that the level of skill in this art is low relative to the difficulty of such a task.

Predictability of the Art.

The invention is directed to treatment of a multitude of diseases with the administration of an androgenic steroid selected from the group consisting of 15-hydroxytestosterones, 16-hydroxytestosterones and precursors thereof. It is well established that "the scope of enablement various inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839 (1970). As an example, the treatment of androgen deficiency could not necessarily be the same for fatigue in HIV.

The Quantity of Experimentation Necessary.

In order to practice the claimed invention, one of skill in the art would have to first envision a combination of an appropriate pharmaceutical carrier, a dosage for each compound, the duration of treatment, route of treatment, etc. and, in the case of human treatment, an appropriate animal model system for one of the claimed compounds. One would then need to test the combination in the model system to determine whether or not the combination is effective for treating each and every disease set forth in claim 31. If unsuccessful, which is likely given the lack of significant guidance from the specification or prior art regarding treatment all of these diseases with an androgenic steroid selected from the group consisting of 15-hydroxytestosterones, 16-hydroxytestosterones and precursors thereof with any compound, one of skill in the art would have to then either envision a modification of the first combination of

pharmaceutical compound, compound dosage, duration of treatment, route of administration, etc. and appropriate animal model system, or envision an entirely new combination of the above and test the system again. If again unsuccessful, which is likely given the lack of significant guidance from the specification or prior art regarding treatment all of these diseases with an androgenic steroid selected from the group consisting of 15-hydroxytestosterones, 16-hydroxytestosterones and precursors thereof with any compound, the entire, unpredictable process would have to be repeated until successful. Therefore, it would require undue, unpredictable experimentation to practice the claimed invention to treat all of these diseases in a mammal by administration of *Genentech, Inc. v. Novo Nordisk*, 108 F.3d at 1366 states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable." Therefore, a method for treatment all of these diseases by administering an androgenic steroid selected from the group consisting of 15-hydroxytestosterones, 16-ydroxytestosterones and precursors of the claims are not considered to be enabled by the instant specification.

Claims 28-31 are rejected under 35 U.S.C. 112, first paragraph, for scope of enablement because the specification, while being enabling for the treatment of androgen deficiency, does not reasonably provide enablement for curatively,

prophylactically, or preventatively treating androgen deficiency as recited in these claims.

The instant claims are drawn to a method of curatively, prophylactically, or preventatively treating androgen deficiency. The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Nature of the invention:

The instant invention pertains to a method of curatively, prophylactically, or preventatively treating androgen deficiency.

The state of the prior art:

The skilled artisan would view that the prevention of one or more symptoms of androgen deficiency totally, absolutely, or permanently, is highly unlikely, since one cannot guarantee that these diseases will always be prevented.

The relative skill of those in the art:

The relative skill of those in the art is very high.

The predictability or lack thereof in the art:

The skilled artisan would view that the treatment to curatively, prophylactically, or preventatively treating androgen deficiency, absolutely, or permanently is highly unpredictable.

The amount of direction or guidance presented and the presence or absence of working examples:

In the instant case, no working examples are presented in the specification as filed showing how to curatively, prophylactically, or preventatively treating androgen deficiency totally, absolutely, or permanently. Note that lack of a working example, is a critical factor to be considered, especially in a case involving an unpredictable and undeveloped art. See MPEP 2164.

Genentech, Inc. v. Novo Nordisk, 108 F.3d at 1366, states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the *Wands* factors, e.g., the amount of direction or guidance provided, absence of working examples, and the predictability of the art discussed

above, to practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation to test the combination in the instant claims whether curatively, prophylactically, or preventatively treating androgen deficiency totally, absolutely, or permanently.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 28-30 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is not clear what disease(s) is/are being treated.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 17, 23, 26, 28, 30, and 31 are rejected under 35 U.S.C. 102(b) as being anticipated by Squibb (FR 2035786).

Squibb teaches a composition and method of use of 16α-α-D-glucoside of 16α, 17-dihydroxysteroid, namely 16α-hydroxytestosterone, in the same manner that estrogen is used in veterinary medicine (claim 1 and 3). The compound is used to inhibit ovulation in warm-blooded animals (mammals) by parenteral administration in doses of 0.1 to 10 mg (page 1, line 38- page 2, line 7).

The prior art teaches the α isomer (species) it therefore anticipates the 16-hydroxytestosterone racemate (genus). *Schering Corp. v. Geneva Pharmaceuticals, Inc.*, 67 USPQ2d 1664.

Thus the limitations of claims 17, 23, 26, 28, 30 are met.

The reference further teaches that said compounds are used to inhibit ovulation, meeting the limitations of claim 31.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 18-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Upjohn Co. (GB 774,064).

Upjohn teaches a number of testosterone derivatives, namely 15-hydroxytestosterone. Furthermore, Upjohn teaches a solution of said compound in an inert solvent (page 1, column 2, lines 43-50).

It would have been obvious to one of ordinary skill in the art at the time of the invention to have known that a solution of 15-hydroxytestosterone is a mixture of its two isomers: 15α-hydroxytestosterone and 15β-hydroxytestosterone. Isolation and separation of isomers of a known racemate is prima facie unless there are "unexpected results," See *In re May,* 197 USPQ 601; *In re Adamson,* 125 USPQ 233; *Brenner v. Ladd,* 147 USPQ 87.

Claim 22 is rejected under 35 U.S.C. 103(a) as being unpatentable over Squibb (FR 2035786) as applied to claims 17, 23, 26, 28, 30, and 31 in further view Wood (Journal of Biological Chemistry, 1983).

Squibb is discussed above. Squibb teaches 16α-hydroxytestosterone.

Squibb does not β isomers of 16-hydroxytestosterone.

Wood teaches 16β-hydroxytestosterone and an aqueous/organic solution thereof (page 8840, experimental procedures; page 8841, figure 1).

It would have been obvious to one of ordinary skill in the art at the time of the invention to have known that a solution of 16-hydroxytestosterone is a mixture of its two isomers: 16α-hydroxytestosterone and 16β-hydroxytestosterone. Isolation and separation of isomers of a known racemate is prima facie unless there are "unexpected results," See *In re May,* 197 USPQ 601; *In re Adamson,* 125 USPQ 233; *Brenner vs Ladd,* 147 USPQ 87.

Claims 17 and 24-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Squibb (FR 2035786) in view of Martin (WO 00/74684).

Squibb teaches 16α-hydroxytestosterone. Squibb also teaches that the 16α-hydroxytestosterone can be formulated with another acceptable supporting pharmaceutical, but does not specifically teach what that agent can be.

Furthermore, Squibb does not teach oral administration or the dose associated with such a route of administration.

Martin teaches pharmaceutical formulations containing various combinations of an estrogen, a progestin, and an androgen for treating postmenopausal and perimenopausal women (abstract; page 2, lines 7-14).

Martin further teaches that the pharmaceutical formulations can be prepared for administration via routes such as oral, intranasal, buccal, ocular, aural, injectable depot, subcutaneous, intraperitoneal, intrauterine, sublingual, or intramuscular routes of administration (page 5, lines 19-24; page 13, lines 28-30).

Martin teaches that regardless of the route of administration, the androgen is typically administered at a daily dosage of 0.01 μg to 5 mg/kg of body weight (page 14, lines 20-23).

It would have been obvious to one of ordinary skill in the art at the time of the invention to have formulated the 16α-hydroxytesterone and additional pharmaceutical agent as taught by Squibb and combined it with estrogen and progestin, as taught by Martin. The motivation is that Squibb suggests an additional pharmaceutical agent and Martin provides the agents estrogen and progestin and in the case of the androgen, one would use 16α- hydroxytestosterone.

Further, it would have been obvious to one of ordinary skill in the art to have combined the active agent, 16α-hydroxytestosterone, as taught by Squibb and formulated it as an oral administration as taught by Martin. One would be motivated to do so in order to increase patient compliance and administrative convenience.

Conclusion

Claims 17-31 are not allowed.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SAHAR JAVANMARD whose telephone number is (571) 270-3280. The examiner can normally be reached on 8 AM-5 PM MON-FRI (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, JEFFREY STUCKER can be reached on (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

JEFFREY STUCKER
SUPERVISORY PATENT EXAMINER